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SENSORIMOTOR NEUROPROSTHETICS

Smell Restoration after brain trauma induced anosmia

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Abstract

Brain injury-induced anosmia, or the loss of the sense of smell due to a traumatic brain injury, occurs when the transmission of information from the olfactory neuroreceptors located in the nasal cavities is not transmitted to the olfactory bulb, due to a section of the nerves. Anosmia reaches one individual out of twenty worldwide, and almost 40% of the cases of anosmia are due to a brain injury. In this report, a device is proposed whose goal is to decode odors sensed with gas sensors and to stimulate the olfactory bulb accordingly. The device is to be implanted in place of the cribriform plate endoscopically. Theoretical as well as practical aspects of this project are reported throughout this report, in order to obtain a performing and most importantly selective nose neuroprosthesis.

1 Introduction

Smelling is the sensation experienced when the olfactory epithelium of the nose is stimulated by volatile substances. In general, it serves an additional dimension of perception to our sensory input. Indeed, a functioning olfactory system enables us to perceive flavors while drinking and eating as well as the appreciation of scents. So, an olfactory disorder generally comes with a gustatory disorder. A working sense of smell also warns us of possible risks or toxins (fire, natural gas leaks in a home or even stale food). Furthermore, Kohli P. et al., 2016 [25], show a reciprocal relationship between olfaction and depression, and thus, the sense of smell contributes substantially to the quality of life.

Hummel T et al., 2017 [22], have analysed 29 papers from various countries about smell loss and have concluded that 5% of the general population suffer from functional anosmia.

There are various causes that lead to olfactory impairment and can be ascribed to one or more mechanisms. One of the main causes is a traumatic brain injury, which is the case for almost 40% of the anosmic patients. A traumatic brain injury will result in the brain hitting the cranial walls, which can cause the section of the olfactory neurotransmitter, thus stopping the transmission and treatment of the odoriferous molecule.

A normal sense of smell is consistent with essential physiological pathways. Indeed, the smell triggers the neuronal receptors of the olfactory epithelium in the nasal upper posterior septum, olfactory cleft and upper parts of the middle and anterior cornea. This produces a neural cascade via the olfactory bulb and ergo, stimulates the olfactory cortex. Any problem in the physiological pathways should affect the sense of smell.

Besides the use of steroid for inflammatory cause of smell loss, the pharmacologic treatments for other causes of anosmia such as head trauma have not yet been proven useful. Konstantinidis I. et al., 2013 [26], have assessed the effectiveness of olfactory training in patients with post-traumatic olfactory dysfunction. They have concluded that 33.2% of the patients recovered the majority of their olfactory function and have also shown the limitations of this approach. Further investigations have demonstrated the possibility to bypass the periphery and to artificially stimulate with an electrode the central regions of the olfactory system.

Artificially stimulating sensory systems is not a novel concept, as one can see with the development and success of cochlear implants. A National Institute on Deafness and Other Communication Disorders (NIDCD) fact-sheet on cochlear implants (CI) says in 2012, the Food and Drug Administration (FDA) estimated that 324'200 people had received implants worldwide. More recently in 2017, around 45'000 CIs are sold worldwide each year, which brings the total number of CI-users worldwide close to 500'000 [45]. Similarly, vision restoration has shown promising results. As in other sensory systems, the pattern of projections of olfactory sensory neurons may provide a topographic map of receptor activation that defines the quality of a sensory stimulus. Therefore, it stands to reason that artificial electrical stimulation of the olfactory bulb could be used as a promising future therapy for anosmia.

Our work is based on Eric H. Holbrook et al., 2019 [19], study that has provided a proof of concept to justify further investigation into artificial electrical stimulation of the olfactory bulbs, to provide olfactory restoration in patients suffering from anosmia.

2 State of the Art Review

No commercially available sensing nose implant currently exists. Unlike vision, olfaction requires a lot of different type of receptors (around 400 for olfaction compared to three (red, green, blue) for vision) which makes it more difficult to design an implant (Weintraub K., 2019 [38]). Indeed, sensors need to be refined so they can discriminate enough odors. Furthermore, 'electronic noses' exist even though the odors are not interpreted by a human brain. Thus, current treatments against anosmia have limited results. When anosmia is the result of an inflammatory cause the most common treatment is steroids but this pharmacological treatment hasn't been proven useful. In the case of a brain trauma injury, there is currently no effective treatment as well. New kind of therapies have emerged, such as olfactory training but again, the efficacy is limited. However, Artificial Electrical Stimulation [19] has the potential to become an efficient therapy. The results were limited and leave room for improvement.

3 Theory

3.1 Presentation

Smell perception results from the activation of the olfactory neuroreceptors located in the nasal cavities via odoriferous molecule. The information is then transmitted to the olfactory bulb. After treatment of the different received action potentials, the signal will be sent to various areas of the brain, namely the piriform cortex, entorhinal cortex, amygdala, hippocampus, the thalamus and finally to the orbitofrontal cortex.

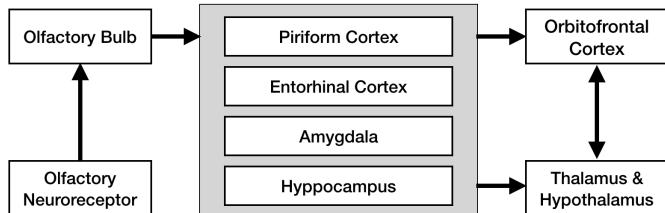


Figure 1 – *Scheme of the transmission of the olfactory information*

Through an odoriferous molecule and with the help of a cognitive process which allows the estimation of the stimuli intensity, it is possible to describe the sensation of smell and some memory linked to it.

3.2 Neuroreceptors

The odoriferous molecules enter the nasal cavities or diffuse in the mouth through the choanae. In both cases, it will reach the olfactory neuroreceptors located at the top of the nasal cavities in the olfactory epithelium.

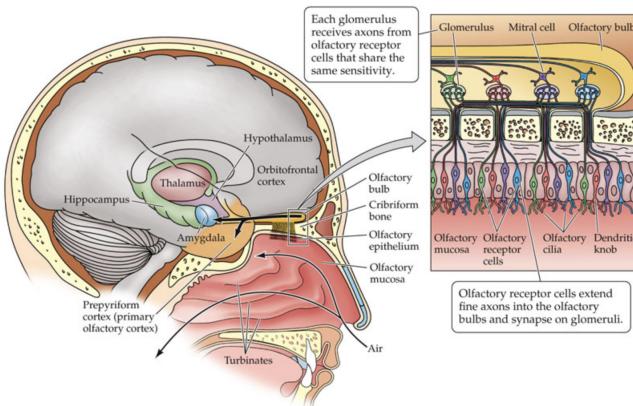


Figure 2 – *Activation of the olfactory epithelium by odorous molecules.* (Watson N.V. et al., 2015 [39])

The neuroreceptors are bipolar neurons with dendritic bathing in the mucus of the olfactory epithelium and fine axons extended into the olfactory bulbs. The detection of the odoriferous molecules happen at the level of the many lashes attached at the end of the dendrites. The membrane of these lashes is full of receptive proteins able to detect the presence of the odoriferous molecules. The activation of one of these proteins comes from the transitory liaison with the odoriferous molecules. This activation will create a sequence of molecular events that will produce an action potential through the axon to the olfactory bulb. The axons are grouped into nerve threads at the base of the epithelium and will transmit the information to the olfactory bulb.

3.3 Olfactory Bulb Treatment

The role of the receptive proteins and the set of neuroreceptors converging on a glomerulus is to indicate the presence of odoriferous molecules through a stimulation pattern. Each odor molecule therefore causes its own glomerular activation map. In each glomerulus, the action potential pattern will produce an increase of glutamate that will depolarize the mitral cell and therefore, produce an action potential in the axons.

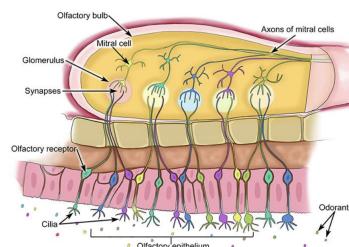


Figure 3 – *Neurosensor detects odor molecules dissolved in mucus in the lining of the nose. The receptors produce action potential in response to odors. The impulses travel via synapses from the sensory neurons to the olfactory bulb. Then, depending on the pattern of the activation, an action potential is created in the mitral cell to the central olfactory system of the brain.* [46]

Glomerulus and mitral cells in the olfactory bulb are the main elements of integration of peripheral signals and play a vital role in detecting and discriminating odorous stimuli.

3.4 Central Nervous System

After the complex preprocessing of the signal into the olfactory bulb, it will be transmitted to the central nervous system (CNS): piriform cortex, perirhinal cortex, amygdala cortex and entorhinal cortex. The hippocampus is also activated thanks to the links with the entorhinal cortex. The initial and direct involvement of the amygdala and the hippocampus could explain the familiar link between smells, emotions and memory: smells can quickly reveal emotions and evoke very old memories. Sela et al., 2009 [36], have shown that focal lesions of the thalamus don't affect odor detection but affect their identification.

3.5 Orbitofrontal Cortex

The information processed by all these structures arrives in the orbitofrontal cortex. It is an integrative cortex involved in the integration of various sensory information, including taste, and participates in decision-making processes. The orbitofrontal cortex is one of the least understood brain regions. The compilation of numerous studies on brain activity and smell made it possible to propose a zone in the orbitofrontal cortex which would be more particularly involved with olfactory information, Gottfried & Zald, 2005 [13]. Concerning the data from the MRI on the

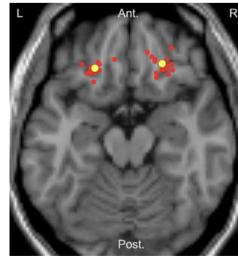


Figure 4 – *Localization of the olfactory orbitofrontal cortex by fMRI imaging. The points in red correspond to the coordinates of the activation peaks observed in 13 studies during an olfactory task. The depth is not represented. The yellow dots indicate the average for each hemisphere of the brain (Gottfriend and Zald, 2005 [13])*

treatment of olfactory information, two remarks should be made. Firstly, the variety of brain activation is weak and much more dispersed than those observed with other senses such as vision. Secondly, these activations are highly fluctuating from one individual to another, under the same observation conditions (Morrot et al., 2013 [31]). This specificity is reflected in the complexity of a nose prosthesis and the need for a case-per-case device.

In addition to the weakness of the brain activity and the diversity between humans, it is important to mention the fact that activation areas depend on the complexity of the odorous substances (Savic et al., 2005 [34]).

3.6 Neurogenesis

Neurogenesis is the process by which new neurons are formed in the brain. Several studies on rats and mice have clearly demonstrated neurogenesis in the olfactory epithelium (Birmingham-McDonogh and Reh, 2011 [3]). All cell types, including olfactory receptor neurons can be regenerated in all species that have been examined.

The globular basal cells produce new olfactory neuroreceptors that extend their axons to the olfactory bulb. The epithelium is restored within four weeks after the injury. In cases of very large olfactory epithelium damage, basal cells proliferate and generate neuroreceptors and other cell types (Graziadei et al., 1980 [14], Graziadei and Monti Graziadei, 1985 [15]).

4 Impairment of olfactory functions

4.1 Presentation

Impairment in the olfactory functions can have several causes and can profoundly influence the patient's quality of life. It can be an issue of transportation of the odoriferous molecules caused by an obstruction of the nasal passages, neurosensory trouble due to lesion of the olfactory neuroepithelium or central olfactory neuronal deficit caused by damage to the CNS. Approximately two-thirds of cases of clinical anosmia are related to upper respiratory tract infections, head trauma and diseases that affect nasal and paranasal sinuses.

Haxel et al., 2008 [17], have shown that 13% of head injuries are associated with a malfunctioning of the sense of smell. Several studies show that the probability of having anosmia depends on the severity of the lesions and can reach 60-70% of cases for severe traumas (Zusho, 1982 [44], Deems et al., 1991 [7]).

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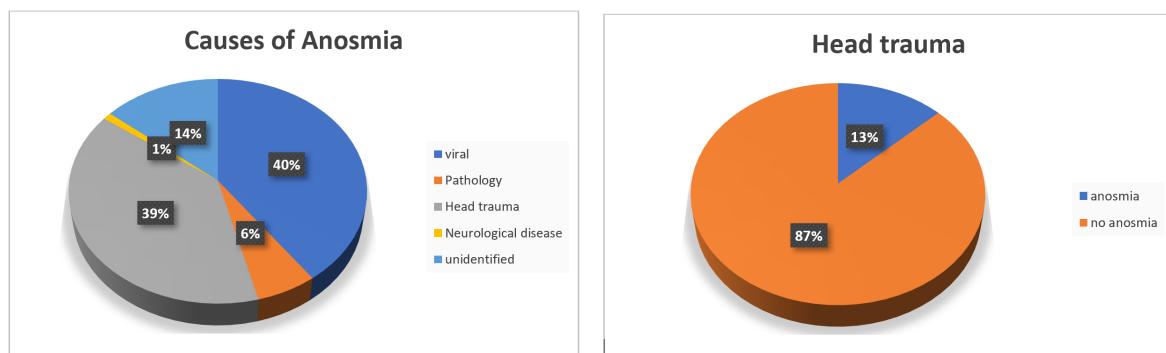


Figure 5 – *Anosmia in numbers* [17]

4.2 Post-trauma

Smell disorder caused by a head trauma can result from impairment at different levels of the olfactory system. The kind of malfunction depends significantly on the location of the cranial

shock. Table 1 summarizes the possible causes of malfunction:

Issue	Malfunction
Obstruction of olfactory clefts	Transport of odorous molecules to olfactory clefts
Section of the axons	Activation of neuroreceptors; or Transmission of the information to the olfactory bulbs
Lesion of the olfactory bulbs	Information processing by the olfactory bulbs
Lesion of the piriform cortex	Transmission to the piriform cortex
Local traumatic injury	Transmission to the different brain regions
Trauma of the frontal lobes	Information analysis, Interpretation, Decision making

Table 1 – *Malfunction description and their causes after a head trauma injury.*

Figure 6 shows the possible mechanisms of impaired sense of smell following a head trauma injury.

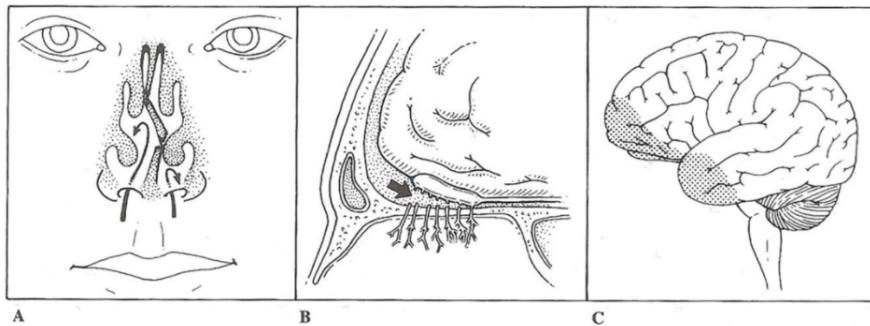


Figure 6 – *Possible mechanisms of impaired sense of smell following head trauma. A: Sino-nasal fractures with obstruction of the passage of air to the olfactory clefts. B: Section of axons of the olfactory neuroreceptors at the level of the screened plate, following the displacement of the olfactory bulbs and the cerebral mass during the shock. C: Cortical contusions and cerebral hemorrhages (from Costanzo et al., 2003 [6])*

4.3 Olfactory Nerve Net Section

The shearing or tearing of olfactory nerve cells is the most common cause of post-traumatic anosmia (Zusho, 1982 [44]). Although studies using animal models show that olfactory receptor cells are capable of regeneration and functional reattachment with the bulb (Graziadei et al., 1980 [14]), olfactory nerve reattachment has not yet been demonstrated in humans. The formation of scar tissue can prevent regenerating axons from crossing the cribbed blade, blocking the reconnection with the olfactory bulb. The possibility of reattachment of the human olfactory nerve is of considerable interest to researchers in the field of neuronal regeneration.

5 Product

5.1 Core odorant categories responsible for most food odors

Recent studies indicate that single cortical neurons integrate signals from diverse odorants. However, a simple question remains, namely, which kind of odorants have signals that are integrated by the individual cortical neurons? Ikue Yoshida et al., 2007 [42] examined the possibility that single neurons could receive signals from different odorants. It is also good to mention that a single odorant can make several neurons shoot action potentials. In their paper, they focused on eight different core food-related categories of odorants. Experimenting on rats, they showed that many neurons were tuned specifically to either one or multiple defined categories. In fact, depending on the composition of the mixture of distinct odor categories, the neurons either showed inhibition or facilitation, hence showing the category-profile selectivity of individual neurons. Following are the eight different categories the researchers decided to focus on:

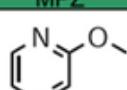
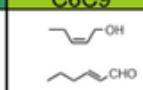
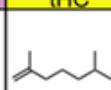
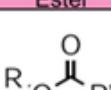
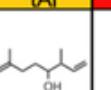
	sulfides	methoxy pyrazines	C6C9 compounds	isothiocyanates	terpene hydrocarbons	esters	terpene alcohols	amines
Sul	MPZ	C6C9	ITC	tHC	Ester	tAI	NH ₂	
structure	R - S - R' R - SH			$\text{R}-\text{N}=\text{C}=\text{S}$				$\text{R} \cdot \text{NH}_2$
components	Dimethyl trisulfide Dimethyl disulfide Diallyl sulfide	2-Isobutyl-3-methoxypyrazine 2-isopropyl-3-methoxypyrazine 2-sec-butyl-3-methoxypyrazine	cis-3-Hexenol trans-2-Hexenal Hexanal (trans,cis)2,6-Nonadienal	2-Propenyl-isothiocyanate isothiocyanate 4-pentenyl-isothiocyanate	α -Pinene α -Limonene α -Phellandrene Myrcene	Isobutyl acetate Isopentyl acetate Isopentyl butanoate Butyl acetate	Linalool Terpineol Citronellol	n-Propyl amine n-Butyl amine n-Amyl amine n-Hexyl amine n-Heptyl amine n-Octyl amine
	onion-like garlic-like	potato-like sweet pepper-like	leaf green cucumber-like	mustard-like radish-like	resin-like citrus-like	fruity banana-like	floral	fishy spoiled food-like

Figure 7 – A panel of odorant categories used for the stimulation.[42]

Our approach will thus be based on this article. As core odorants can be classified into 14 different categories, according to Fig.8 and [47], based on their molecular structure and perceptual quality, they suggest that the odor of individual foods can be characterized basically by either a single odorant category or a specific combination of these categories. Based on this, we can assume the same principles can be applied for other kind of odors like gases in general.

Thus, the main goal of the neuroprosthesis developed is to be able to detect potentially harmful or dangerous gases and then transmit the signal sent by the gas molecules' receptors to the electrodes placed inside the nose, so as to electrically stimulate the cortical neurons linked to their specific category or categories.

	Sul	alcohol	MPZ	C6C9	aldehyde	ketone	ITC	tHC	Ester	tAl	NH2	acid	lactone	phenol	
	R-S-R	R-SH	R-OH			R-CHO		R-NiCS							
onion	a														
garlic	b	c													
shallot	d														
asparagus	e														
leek	f	g	h		i										
tomato	j	k	l	m								n			
cabbage	o	p	q	r	s	t									
carrot		u	v	w											
beet	x	y													
potato	z	aa		ab											
lettuce		ac													
sweet pepper		ad	ae	af											
celery		ag					ah	ai	aj	ak					
raddish					al										
horse raddish					am										
grapefruit	an			ao											
apple		ap					aq								
loquat	ar	as	at	au			av								
banana	aw	ax					ay					az			
grape		ba					bb								
melon		bc					bd								
kiwi fruit		be					bf								
cherry	bg	bh	bi	bj			bk	bl							
orange		bm	bn			bo	bp								
strawberry		bg					br	bs							
pineapple	bt		bu	bv			bw	bx				by			
plum			bz				ca	cb				cc		cg	
mandarin			cd			ce	cf								
lemon			ch			ci									
pear							cj								
raspberry				ck					cl						
apricot	cm		cn						co		cp			cr	
peach									cq						

Figure 8 – *Odorant-category profiles of 33 natural foods.* [42]

As mentioned in Holbrook E.H. et al.’s work, 2019 [19], it is possible to electrically stimulate the olfactory bulb. To do so, electrodes need to be placed endoscopically into the paranasal sinuses as shown in Fig.9 to stimulate the olfactory bulb. The principle is the same as a cochlear implant. Despite the fact that three out of five patients succeeded in smelling something due to the electrodes’ stimulation, the odors they perceived weren’t pleasant. The descriptions of their smelling sensations are imprecise but it is likely because they reflect the rather blunt and imprecise methods of monopolar stimulation used in Holbrook E.H et al., 2019 [19]. As said in the article, the method used here for stimulation probably activates multiple glomeruli and neurons simultaneously, with sensations similar to the aberrant sensory experience in pathological cases of phantosmia or dysosmia resulting in abnormal smelling sensations (Hong S.C. et al., 2012 [20]).

Hence, in order to avoid this discomfort, our device has micro arrays as electrodes, to prevent that a single electrode covers and activates multiple neurons at the same time thus creating uneasiness. The neurons have to be specifically targeted depending on their odorant category and the odor molecules received so as to get accurate and fine-tuned sensations. Solid State Electrochemical gas sensors are chosen for their high selectivity as the nose doesn’t have a closed and controlled environment (any gas can enter the nose cavities), as can be seen in Section 5.4.2.

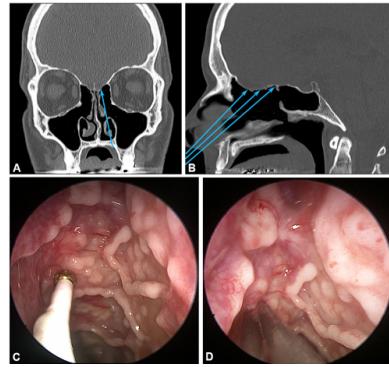


Figure 9 – *Stimulating electrode positions.* (Holbrook E.H et al., 2019 [19])

5.2 Product design

In order to avoid the discomfort mentioned previously, the device has micro arrays as electrodes, to prevent that a single electrode covers and activates multiple neurons at the same time. The neurons have to be specifically targeted depending on their category and the gas molecule received to get accurate and fine-tuned sensations. Sensors for different gas molecules are placed on the opposite side of the device where there are no electrodes. A microprocessor is embedded into the device to process the information received from the sensors and to activate the electrodes accordingly to the neurons they are linked to. A wire connects the device to an external battery to power it. Sketches of the device can be seen in Fig.10.

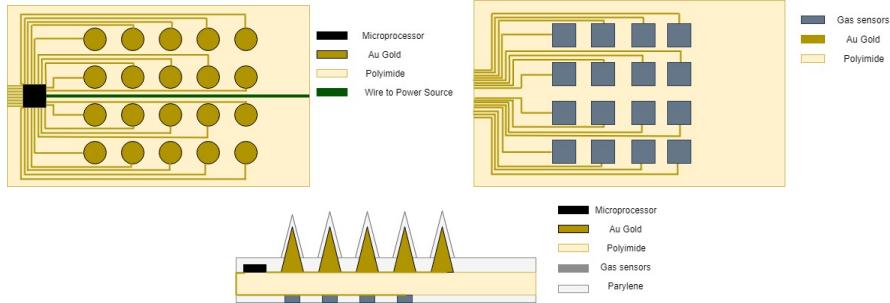


Figure 10 – *Device Design.*

5.3 Product placement

The device would 'replace' the cribriform plate (CP). Each electrode of the device should be in contact with the nerve fibers as seen in Fig.11.

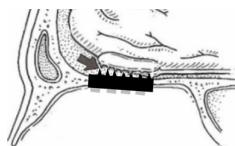


Figure 11 – *Device Placement*

The cribriform plate has an average length of 21.28 mm and an average width of 4.53 mm (Coelho D.H. et al., 2018 [5]). There is a range of both length and width of the CP between individuals, particularly concerning width. In practice, all of this emphasizes the importance of pre-operative imaging and recognition of anatomic variability for surgical procedures. Indeed, the CP being different in size for each individual, pre-operative imaging would allow us to be as general as possible, and our device should be adaptable on a case to case basis.

5.3.1 Surgery

Our device is placed in contact with the olfactory bulb via an endoscopic procedure. By entering through the nasal cavity, the surgeon removes the olfactory nerves that were sectioned. The cribriform plate is then drilled and the foramina removed as shown in figure 12.

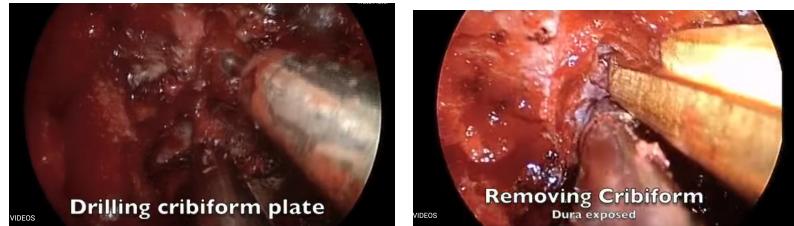


Figure 12 – *Operation for cribriform plate removal. [49]*

Once the cribriform plate completely removed, the arrays of our device are carefully put in contact with the nerves on the olfactory bulb. The device is drilled and clipped in place of the cribriform plate. Particular attention should be paid to the main problem that occurs when drilling the cribriform plate, which is leakage of Cerebrospinal fluid. The device will, therefore, be hermetically adapted to fit the bone structure.

Note that the device described in this report corresponds to a general product and has to be adapted case per case. By using scanners, we can know accurately the position of the foramina and thickness of the cribriform plate and thus place our electrodes and general device accordingly, depending on the person.

5.4 Selectivity

One essential point of our product relies on its selectivity. It is needed to sense the correct odor and stimulate the corresponding nerve. To achieve and optimize such selectivity, three main components that ought to be considered were identified. First, the selectivity related to the electrodes placed on the olfactory bulb, second the type of gas sensors and last but not least, the brain imaging techniques used during the trials.

5.4.1 Electrodes

Different electrode arrays were considered. In order to achieve maximal precision, micro fabricated electrodes were opted for.

As the perception of odorant relies on interactions between cells, microelectrode arrays help overcome the limitations of single microelectrodes by allowing easy simultaneous stimulation (Lehmkuhle M.J., 2003 [27]). Such microelectrode arrays (MEAs) consist for example of Utah arrays, constructed in silicon and coated with platinum to facilitate the charge transfer. Nanoelectrode arrays (NEAs) were also considered as they do less damage to neurons, therefore limiting the risk for inflammations and are more precise.

Finally, it was important to opt for a more flexible MEA, because as opposed to most MEAs such as Utah arrays, a flexible structure is less invasive as it allows the electrodes to fit and adapt to the surface of the brain (Bahareh G.M. et al., 2013 [2]). A polymer is typically used as structural substrates. In our case, polyimide was used for the substrate and the flexible MEA structure was encapsulated with parylene due to its biocompatibility. The electrode are made of gold and coated with carbon nanotubes for enhanced electrical simulation of neurons.

5.4.2 Gas sensors

As more than 400 types of receptors can be counted in humans which allow us to smell more than 1 trillion different odors (Morrison, J., 2014 [30]). Selectivity and accuracy when it comes to the gas sensors employed is therefore essential for our device's success. The first limitation for the chosen gas sensor comes with the size of our device and its endoscopic placement.

Three main gas sensor types were considered (Hu W. et al., 2018 [21]):

- **Chemoresistive Gas Sensor:** This gas sensor induces a change in electrical resistance in response to chemical environment, as the gas molecules adsorb on the surface and react with active oxygen species. Free electrons are liberated in the bulk, which lowers the potential barrier, electrons flow more easily and therefore reduce the electrical resistance. (Neri G., 2009 ??)
- **FET-Based Gas Sensor:** The principle of a FET sensor relies on the flow of carriers: the gas molecules change the nature of the conductive channel of the FET and therefore change the electrical characteristics (Yang S. et al., 2017 [41]).
- **Solid State Electrochemical Gas Sensor:** these sensors regroup equilibrium potentiometric sensors (EPS), mixed potentiometric sensors (MPS), amperometric and impedance-metric gas sensors. The interaction between the sensor's material and the gas read as a measurable electrical signal.

Finally, a Solid State Electrochemical Gas Sensor was opted for, due to its stability and as it allows for a selective and accurate sensing. Amperometric electrochemical Gas Sensors based on solid electrolytes (galvanic cells) are therefore used throughout this project: they have the advantage of being small and lightweight, and allow to detect leakage of dangerous (toxic or inflammable) gases (Azad A.M., 1992 [1]). The gas sensor can be purchased directly [51].

5.4.3 Brain imaging

The brain imaging method selected for the experimental plan and data collection plays a major role when it comes to the selectivity evaluation of our device. First, a functional method is opted for, as we wish to measure the brain activity of the patient whilst he is asked to smell different odor sets.

Both direct methods (measure of electrical signals) and indirect methods (measurements of blood flow) are considered. When it comes to the direct methods, the first explored was EEG as it has a good temporal resolution and allows for a relatively fast response with a low cost. However, it is not optimal for our application as its poor spatial resolution cannot respond to the selectivity desired. Also, EEG measurements are high in noise and poor in accuracy. A non-invasive method is thus chosen, which puts aside ECoG or MUA/SUA.

Finally, MEG was chosen due to its several advantages over EEG and the previously mentioned methods: notably for its good temporal and spatial resolution.

When it comes to indirect methods, the best spatial resolution was given by fMRI and PET. NIRS only ensures a low penetration level and a poor spatial resolution and was therefore not considered further. fMRI was chosen over PET as PET has quite a high cost and some safety restrictions. However, fMRI is limiting due to its relatively low temporal resolution, but this problem can be overcome by adapting our experimental plan.

To sum up, the final experiments would be conducted with both MEG and fMRI, in order to ensure optimal conditions for good spatial resolution and selectivity.

5.5 Microprocessor and power supply

5.5.1 Olfactory processor

Schild D., 1988 [35], proposed a concept of olfactory coding describing the stimulus responses of receptor cells using vector spaces. He showed how the network of the olfactory bulb succeeds in discriminating odors with high selectivity. Hence, we will base the coding of the microprocessor on it as shown in Fig.13.

5.5.2 Power supply

By optimizing the electrical implanted circuits, the power consumption is reduced. The implant battery will charge through the nose via an external nose clip which will have to be worn while the patient sleeps. It will charge with inductive coupling, without a need for surgery or wiring (Sole M. et al., 2011 [37]).

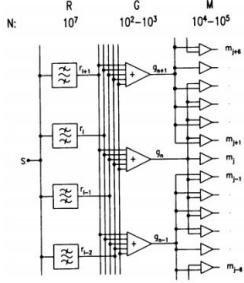


Figure 13 – *Block diagram of information flow from stimulus to mitral cells. A 1-D simplified model without interneurons is shown. S is the stimulus. Receptor cell classes are shown as filters. The connections between receptor cell classes and glomeruli (G) have a data bus structure. r is the activity of the l-th receptor class. g is the overall input activity of the n-th glomerulus. The connections between glomeruli and mitral cells (M) are local data buses so that a glomerulus gives input to mitral cells in its neighborhood only.* [35]

6 Materials and Manufacturing Process

6.1 Substrate and Encapsulation

One of the most important constraint of an odorant sensor in biomedical applications is the need for protective bio-compatible and impermeable layers. Furthermore, our device should be flexible to allow, among others, more ease during the surgical procedure, better adeptness to the topography of the cribriform plate (which may differ from one person to another and is not flat) and to avoid any discomfort or unwanted mechanical constraints that may either damage the device or the patient’s tissues. Potential material choices that meet such requirements for flexibility and bio-compatibility include polyimide, parylene and SU-8. Parylene C is a well-characterized polymer that is used mainly as an encapsulation material, especially for biomedical applications since it is inert, bio-compatible and bio-stable; it is also an excellent barrier to both liquids and gases (Martins I.O., 2017 [28]). Other properties of interest of parylene C include its flexibility, bendability, conformability and superior resistance to moisture absorption (0.06 %) (Prouza A.N.A., 2015 [33]). Parylene C could also serve well as a substrate because of its compatibility with a variety of other materials (Meng E. et al., 2015 [29], Yu H. et al., 2008 [43]).

Polyimide has many advantageous properties including high Young modulus, good chemical resistance, high hydrolytic stability, adhesive properties, a low dielectric constant and high thermal stability (Ghosh M.K. et al., 1996 [12], Chang W.Y. et al., 2008 [4]). Polyimide has a much higher tensile modulus (8830 MPa) than Parylene C (20 MPa) and is more robust for sensor development (Prouza A.N.A., 2015 [33]). Besides mechanical and thermal stability, other important factors to consider include manufacturing reproducibility and tolerance to contaminants. Polyimide thin films are produced by spin coating. Polyimide is therefore chosen as a substrate, and Parylene for the encapsulation. As our device is to be put in place of the CP, it needs to ensure rigidity. In that purpose, Hydroxyapatite powder [52] will be injected in the Polyimide substrate.

6.2 Metal Electrodes

Gold is a metal with high chemical inertness, is bio-compatible and at this scale not toxic. We will use gold/titanium electrodes on our device. In this case, the Titanium will act as a adhesive to more effectively bound the metal to the substrate. We then encapsulate this metal array with a thin layer of Parylene, of $5\mu\text{m}$ thickness.

7 Data collection

7.1 Experimental Recordings

In order to test our product and follow the patients, a clinical trial testing is needed. First, a baseline ought to be established to judge of the validity of the trial. An accurate protocol needs to be written and should take into account the different parameters that might influence the sense of smell and the results of the study. An olfactory map ought to be established by recording brain activity in healthy subjects and with literature.

7.1.1 Baseline

The baseline will consist of healthy subjects, but also of patients with anosmia but that were not yet treated. Our goal is to test over 100 healthy subjects and over 50 with anosmia, both female and male, and belonging to different age groups.

What we want is an 'odor map' of the brain to try to see which neurons activate which part of the brain depending on the odor, in order to increase selectivity. The odor map will be made from the healthy sample, the one without anosmia, to ensure a completely functioning olfactory system by removing the uncertainty of a damaged or degenerated olfactory bulb. Moreover, this could allow us, in theory, to observe a very similar map in the healthy population for all individuals. As in anosmic people the map could vary greatly because the way people are affected by anosmia can be different from one person to another, this explains why the odor map should be constructed from healthy samples.

7.1.2 Data Acquisition

A set of odorants is created, regrouping different food and natural elements. Past research demonstrated a neural connectivity of the olfactory cortex, with the hippocampus and thus related to the connection between smell and memory (Herz, R.S. et al., 1996 [18]).

Every patient is asked to recognize the different odors, while imaging their brain activity in order to achieve a good selectivity.

We opt for a functional imaging method. The most common imaging technique for odor mapping in the olfactory bulb is first fMRI, with previous studies performed on mice.

MEG is also used, as it has a high temporal resolution and can be used as an imaging technique in olfactory research. MEG also allows detection activation in deep structures.

8 Result Analysis

8.1 Data Analysis

In order to analyze the data, we will need to collect and preprocess it by denoising and comparing signals for healthy and unhealthy subjects. As the datasets are large, noisy and richly structured, their analysis needs to rely on a broad range of mathematical and signal processing tools (Matlab, Java, Python etc.). Our signal processing will include linear regression (mass univariate models), multivariate models (Principal Component Analysis, partial least squares, independent component analysis), pattern recognition (machine learning) and graphical models.

The goal is to look for patterns and different activations depending on task/odor, focusing on the following points:

- Comparison of the patterns of brain activity between anosmia treated, non-treated and healthy subjects.
- Comparison of the response to the different odors (pleasant, unpleasant, neutral).
- Comparison of the data measured with different functional imaging techniques (MEG, fMRI).
- As we want to have follow-up trials (after the surgery), we also want to see for how long after the medical procedure, the patient presents sensing patterns.
- Comparison of the data measured between both sexes and between different age groups.

8.2 Optimization

The optimization of our product will occur through the analysis of the obtained results. It will consist on both a better placement of the product and of the electrodes in contact with the olfactory bulbs, as well as optimizing the selectivity by exploring different tools. It is important to have a solid baseline and then adapt our product case per case by imaging and preparing the patient before the surgery.

By performing several check-ups and experiments post-surgery, the patient will be assisted in the process of learning and recognizing the odors.

9 Discussion

The proposed implemented device consists of Solid State Electrochemical Gas Sensors which decode the odor molecules and transmit the information to the olfactory bulb through electrodes. The main limitation comes from the complexity of the human olfactory system, which requires an excellent selectivity of our device: it needs to sense the correct odor and stimulate the corresponding nerve. The microelectrode arrays placed on the olfactory bulb, the electrochemical gas sensors, fMRI and MEG brain imaging, the materials and dimensioning choices of our device all play a major role in the correct functioning of the prosthesis and were selected accordingly.

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A Clean room process flow

A proposition of process flow for our device is proposed hereafter.

Step	Process description	Cross-section after process
01	Substrate Preparation Pro : SpinCoating of polyimide and Equ : PHOTOPRO33(Z12) Thi : PI (4.53 mm) Rem: /	
02	Deposition of the photoresist Pro : Lamination of ordyl (PR) Equ : PHOTOPRO33(Z12) Thi : 20 µm Rem: /	
03	Exposition of the photoresist Pro : Photolithography Equ : Süss MJB4 (Z13) Thi : / Rem: /	
04	Development of the photoresist Pro : Photolithography Equ : Base wetbench (Z13) Thi : / Rem: /	
05	Metal deposition Pro : Evaporation Equ : EVA760 (Z11) Thi : Ti=10nm Rem: /	
06	Lift-off Pro : Resist stripping Equ : SVC14 (Z13) Thi : / Rem: /	
07	Deposition of the photoresist Pro : Lamination of ordyl (PR) Equ : PHOTOPRO33(Z12) Thi : 100 µm Rem: /	
08	Exposition of the photoresist Pro : Photolithography Equ : Süss MJB4 (Z13) Thi : / Rem: /	
09	Development of the photoresist Pro : Photolithography Equ : Base wetbench (Z13) Thi : / Rem: /	
10	Metal deposition Pro : Evaporation Equ : EVA760 (Z11) Thi : Au=100 µm Rem: /	
11	Lift-off Pro : Resist stripping Equ : SVC14 (Z13) Thi : / Rem: /	
12	Encapsulation Pro: Parylene coating Equ: COMELEC C-30-S (Z10) Thi: 5 µm Rem: /	

Figure 14 – *Step-by-step process flow outline of our device.* Pro: process , Equ = équipement, Thi = Thickness, Rem = Remark